Stereotactic and hypofractionated radiotherapy for high risk lung tumors

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Chapter 4

Outcomes of hypofractionated high dose radiotherapy in poor-risk patients with "ultracentral" non-small cell lung cancer

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ABSTRACT

Introduction

We defined "ultracentral" lung tumors as centrally located non-small cell lung cancer with planning target volumes overlapping the trachea or main bronchi. Increased toxicity has been reported after both conventional and stereotactic radiotherapy for such lesions. We studied outcomes after 12 fractions of 5 Gy (BED_{10} = 90 Gy, heterogeneous dose distribution) to ultracentral tumors in patients unfit for surgery or conventional chemoradiotherapy.

Methods

Clinical outcomes and dosimetric details were analyzed in 47 consecutive patients with single primary or recurrent ultracentral non-small cell lung cancer treated between 2010 and 2015. Those irradiated previously or with metastasis to sites other than the brain and adrenal glands were excluded. Treatments were delivered using volumetric modulated arc therapy.

Results

Median age was 77.5 years, 49% of patients had a World Health Organization performance score of 2 or higher, and the median planning target volume was 104.5 cm^3 (range 17.7-508.5). At a median follow-up of 29.3 months, median overall survival was 15.9 months, and 3 years survival was 20.1%. No isolated local recurrences were observed. Grade 3 or higher toxicity was recorded in 38%, with 21% scored as having a "possible" (n = 2) or "likely" (n = 8) treatment-related death between 5.2 and 18.2 months after treatment. Fatal pulmonary haemorrhage was observed in 15% of patients.

Conclusions

Unfit patients with ultracentral tumors treated using this scheme had a high local control and a median survival of 15.9 months. Despite manifesting rates of a fatal lung bleeding comparable to that seen with conventional radiotherapy for endobronchial tumors, the overall rate of grade 5 toxicity is of potential concern. Additional work is needed to identify tumor and treatment factors related to haemorrhage.

INTRODUCTION

Centrally located lung tumors pose a treatment challenge in patients who are unfit to undergo chemo-radiotherapy, the standard of care in locally advanced non-small cell lung cancer (NSCLC).[1,2] Many elderly patients are unfit for chemoradiotherapy. Population studies show that high-dose radiotherapy (RT) alone is used in 11 to 41% of elderly patients with stage III NSCLC, while 21 to 27% receiving no anticancer treatment, resulting in median overall survivals (OS) of 7.6 and 6.9 months, respectively.[3–5] As the requirement for travel for 4 to 6 weeks to undergo conventional radiotherapy may discourage frail patients, shorter hypofractionated radiotherapy regimens have been advocated.[1,6]

Stereotactic ablative radiotherapy (SABR) is the current standard of care for unfit patients with peripheral lung cancers, and has been defined by delivery of a BED_{10} (biologically effective dose with an α/β ratio of 10) of at least 100 Gy. With limited data available, however, European Society of Medical Oncology guidelines suggest more conventional radiotherapy for large tumors or central NSCLC instead of SABR.[7,8] Furthermore, central tumors have an increased risk for haemorrhage.[9–12] The term "ultracentral" has been used to describe tumors in cases in which the gross tumor volume (GTV) directly abuts the major airways.[13] However, our clinical practice defines an ultracentral lesion where a planning target volume (PTV) overlaps the trachea or main bronchi, and should be distinguished from moderately central tumors, which are adjacent to central structures.[14]

In 2010, we introduced a hypofractionated schedule delivering 12 once-daily fractions of 5 Gy over approximately 3 weeks (prescription BED_{10} = 90 Gy to 95% of the PTV; BED_3 = 160 Gy at the periphery, with higher doses inside the PTV), for patients presenting with ultracentral or large peripheral tumors who were assessed by a multi-disciplinary tumor board (MDT) to be unsuitable for SABR, or either unsuitable for, or unwilling to undergo conventional chemoradiotherapy or surgery. Our aim was to provide a patient-friendly treatment for poor-risk patients, with use of small PTV margins, online image guidance, and volumetric modulated arc therapy (VMAT), all of which would reduce doses to organs at risk (OAR). This manuscript describes our experience with ultracentral lung tumors.

MATERIAL AND METHODS

Patient selection and definitions

Patients at our institution who present with local or locoregional NSCLC are discussed at MDT meetings, or are referred after discussion in an external multi-disciplinary tumor board. Poor-risk patients who were not candidates for standard curative-intent therapies and in whom the

PTV overlapped the trachea or main bronchi (i.e., ultracentral), were treated using 12 fractions of 5 Gy (Supplemental Table 1). In individual cases, some ultracentral tumors were accepted for eight fractions on the basis of clinician judgment, typically because of limited PTV-main airways overlap.[14] The latter group of patients were excluded from the present analysis.

An institutional database was queried to identify patients treated using 12 fractions of 5 Gy for either a single primary or recurrent ultracentral NSCLC between 2010 and 2015. Patients with previous thoracic irradiation or presenting with metastasis to sites other than the brain or adrenal glands were excluded. Tumor stage was determined on the basis of the diagnostic positron emission tomography-computed tomography (PET-CT) and planning CT scans by using the 7th edition of the tumor, node, and metastasis (TNM) system. Primary tumor diameters were defined as the greatest dimension on the axial, frontal or sagittal plane in one phase (end inspiration) of the planning CT scans. All of the pretreatment imaging scans were retrospectively evaluated by a pulmonologist specialized in interstitial lung diseases (ILD) to identify the presence of radiological signs of ILD.

Treatment planning and delivery

Treatment planning and delivery techniques were as previously described for SABR at our center.[15,16] In cases in which tumors overlapped hilar structures, a second four-dimensional CT (4D-CT) scan was occasionally performed after administration of intravenous contrast. Some patients also underwent a 4D PET-CT scan. Treatment planning was performed on the average intensity projection (Ave-IP) of the 4D CT scan. The prescription dose was 60 Gy delivered in 12 fractions (BED_{10} = 90 Gy), at four fractions per week over 3 weeks. Our institutional protocol required that 95% and 99% of the PTV received 100% and 90% of the prescription dose, respectively. A PTV maximum point dose (D_{max}) of no more than 140% of the prescription dose was recommended. Guidelines for OAR were a point D_{max} of 32 Gy for the spinal canal, 48 Gy for the esophagus, and 42 Gy for the brachial plexus. PTV underdosage was allowed to avoid exceeding these limits. There were no specific dose limits for the heart, trachea, and main bronchi. Coplanar VMAT plans were delivered using two RapidArc (Varian Medical Systems, Palo Alto, CA) arcs.[16] Online setup on the tumor was performed by using a conebeam-CT.

Clinical outcomes

Clinical follow-up was generally performed 3, 6, 12, 18, and 24 months after treatment and yearly thereafter, with a diagnostic CT scan done at each visit. In patients who were frail and/or lived some distance away from our center, follow-up was performed by telephone combined with information from referring physicians and general practitioners. Survival data were updated using Dutch civil records. Available patient data from institutional records, referring hospitals, and general practitioners were used to retrospectively evaluate

disease control and toxicity. Evaluation of local recurrences and toxicity was done by at least three physicians (including two radiation oncologists), and was consensus based. Local recurrences were defined as tumor progression within the radiation field on follow-up radiological imaging. Severe toxicity (i.e. grade 3 or higher) was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Potential fatal toxicity (G5) was subclassified into a "possible" or "likely" treatment-related death, and these cases were also independently evaluated by two pulmonologists. In cases in which the relationship of an adverse event with treatment could not be excluded, these events were scored as toxicity. Only the highest grade of an adverse event, with corresponding date, was reported for each patient.

Dosimetric data

OAR were retrospectively delineated, when required, on the Ave-IP in the Eclipse Treatment Planning System (Varian Medical Systems, Palo Alto, CA) for dosimetric analysis. The lumen of the entire main bronchus was contoured in both mediastinal and lung settings, after which a 3-mm expansion was added to encompass the outer bronchial wall. The same procedure was performed for the tracheal wall, which was contoured 2 cm craniocaudally to the PTV. The esophagus was also contoured 2 cm craniocaudally to the PTV and expanded using at least two phases of the 4D-CT. Lung contours were automatically generated with subtraction of the PTV for dosimetric analysis. The new or edited contours could result in differences in dose-volume histograms (DVH) with respect to the clinical plan. We report on maximum point doses (D_{max} in Gy), minimum doses received by small OAR volumes (D_{xcc} in Gy), and volumes of lung receving x Gy or more (V_{xGy} in percentages).

Statistics

Statistical analysis was performed using IBM SPSS for Windows, version 20.0 (IBM, Armonk NY). Median follow-up time was calculated with the reverse Kaplan-Meier method and the time-to-event outcomes were calculated with the Kaplan-Meier method.[17] The date of first radiation treatment was defined as day 0 of follow-up. Continuous dosimetric parameters were compared between patients with or without G3 or higher toxicity by using the independent sample *t* test and the Mann-Whitney U test.

RESULTS

Patient and tumor characteristics

A total of 47 patients with ultracentral tumors were identified (Table 1). Figure 1 shows two examples of treated ultracentral tumors. Malignancy was not pathologically-proven in 11 patients (23%). In the latter group, no biopsy was performed on account of bleeding during

Table 1 - Patient and tumor characteristics

Characteristic	Number of patients (%) or median value (range)
Age at start of index RT, years	77.5 (57.7-90.8)
Female gender	12 (26%)
History of COPD	34 (72%)
GOLD I / II	6 (13%) / 14 (30%)
GOLD III / IV	10 (21%) / 4 (9%)
WHO performance score	
0 / 1 / 2 / 3	6 (13%) / 18 (38%) / 21 (45%) / 2 (4%)
Age-adjusted Charlson comorbidity index	
4-5	4 (9%)
6-7	31 (66%)
8-9	9 (19%)
10-11	3 (6%)
Prior non-lung malignancy	14 (30%)
Prior lung surgery	10 (21%)
Single lung	2 (4%)
Pathological diagnosis of malignancy obtained	36 (77%)
Adenocarcinoma	6 (13%)
Squamous cell carcinoma	23 (49%)
Adenosquamous carcinoma	2 (4%)
NSCLC NOS	3 (6%)
Carcinoma in situ / squamous dysplasia, suspicious for invasive growth[a]	2 (4%)
Endobronchial tumor location[b]	
Endobronchial tumor present	25 (53%)
Endobronchial tumor absent	5 (11%)
Unknown endobronchial tumor status	9 (19%)
[^{18}F]FDG-PET staging	47 (100%)
Disease stage (TNM 7th)	
Stage IA / Stage IB	1 (2%) / 3 (6%)
Stage IIA / Stage IIB	3 (6%) / 14 (30%)
Stage IIIA	18 (38%)
Recurrent NSCLC	8 (17%)
Presence of nodal disease	14 (30%)
Peribronchial or hilar nodes (N1)	11 (23%)
Mediastinal nodes (N2)[c]	3 (6%)
Tumor diameter, cm	5.6 (1.3-12.0)
Tumor diameter >5 cm	28 (60%)
Tumor diameter >7 cm	15 (32%)
ITV / PTV, cm^3	45.1 (4.7-336.5) / 104.5 (17.7-508.5)
PTV location	
Overlap with main bronchus	44 (94%)
Overlap with trachea	20 (43%)
Overlap with both trachea and main bronchus	17 (36%)

Table 1 - Patient and tumor characteristics (*continued*)

Characteristic	Number of patients (%) or median value (range)
Prior treatment for index lesion	10 (21%)
Endobronchial treatment	4 (9%)
Chemotherapy	2 (4%)
Sleeve lobectomy	1 (2%)
Surgery with adjuvant chemotherapy	3 (6%)
Systemic therapy for index lesion	
<6 months before index RT[d]	1 (2%)
<6 months after index RT	-
Thoracic re-irradiation after index RT	4 (9%)

[a]One patient had a recurrence after sleeve lobectomy and adjuvant chemotherapy. [b]Eight patients had an ultracentral PTV owing to a lymph node and were not scored for the presence of an endobronchial tumor. [c]One patient had both N1 and N2 disease. [d]Patient received carboplatin/gemcitabine for up to 1 month before the start of radiotherapy. Abbreviations: COPD = chronic obstructive pulmonary disease; [^{18}F]FDG-PET = fludeoxyglucose F 18 positron emission tomography; GOLD = Global Initiative for Obstructive Lung Disease; ITV = internal target volume; PTV = planning target volume; RT = radiotherapy; TNM = tumor, node, and metastasis cancer staging of the American Joint Committee on Cancer; WHO = World Health Organization.

bronchoscopy in two cases, bronchoscopy was terminated due to clinical deterioration in three others, and malignancy could not be proven on the biopsy specimen in four cases. Disease was classified as stage I in 9%, stage II in 36%, and stage IIIA in 38% of patients, and in 17% the treated lesion was a recurrence ("recurrent NSCLC"). Before the start of thoracic radiotherapy, one patient had metastatic disease due to an adrenal metastasis. This patient was classified in the group of recurrent NSCLCs because the treated lesion represented a recurrence. Median age was 77.5 years (range 57.7-90.8), and 49% had a World Health Organization performance score of 2 or higher. The median Charlson comorbidity index (CCI) was 4 (range 2-8), and when corrected for age, 7 (range 4-11). The (co)morbidities contributing to the CCI were cancer (100%), chronic pulmonary disease (77%), diabetes mellitus (23%), peripheral vascular disease (21%), and myocardial infarction (11%). Four patients (9%) were retrospectively assessed to have non-classifiable interstitial radiological changes that did not fulfill the formal criteria of idiopathic pulmonary fibrosis (IPF). Antiplatelet drugs and oral anticoagulants were used by 38% and 13% of patients at referral, respectively.

All patients completed treatment in a median of 21 days (range 16-34). Median total PTV was 104.5 cm^3 (range 17.7-508.5 cm^3), and tumor diameter exceeded 5 cm in 60% of patients. The PTV included nodal disease in 30% of patients, and in 17% (n = 8), ultracentral was defined by location of a lymph node. Besides the ultracentral tumor location, proximity of PTV to the esophagus was also a contributing factor leading to the choice of a 12-fraction schedule in 64% of patients. Similarly, both ultracentral location and large target volume influenced the choice of scheme in 38% of patients. For the latter, the median internal target volume (ITV) was 85.7 cm^3, and the median tumor diameter was 7.8 cm.

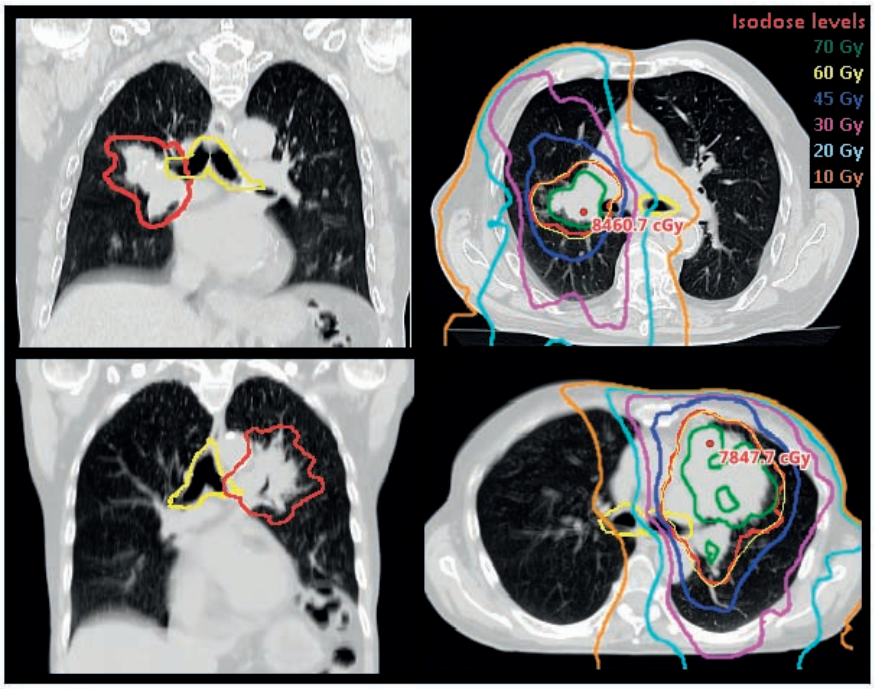


Figure 1 - Examples of ultracentral tumor locations (PTV in red and trachea/main bronchi in yellow) with their dose distributions.

Overall survival and disease control

Median follow-up for survival was 29.3 months (95% CI 21.5-37.1). Median OS was 15.9 months (95% CI 11.2-20.6). The 1, 2, and 3 years OS rates for all stages were 61.5%, 28.7%, and 20.1%, respectively (Figure 2). Median OS was not reached for stage I, and it was 15.9 months (95% CI 8.5-23.3) for stage II, and 10.4 months (95% CI 7.7-13.1) for stage IIIA. Mortality rates after 30, 90, 120, and 180 days were 0%, 0%, 2%, and 9%, respectively.

At 12, 18, and 24 months of follow-up, one or more follow-up CT scans were performed in 85%, 80% and 78% of patients who were still alive, respectively. In total, 94% (n = 44) of patients had one or more follow-up CT scans, with a median follow-up time for CT imaging of 24.1 months (95% CI 22.5-25.8). The remaining three patients survived 3.5-11.6 months.

Disease progression was recorded in 30% of patients (n = 14), with a median time to relapse of 29.5 months (95% CI 20.1-38.9) for all stages (Figure 2). There were no cases of an isolated local recurrence. An isolated locoregional recurrence was seen in 2% of patients.

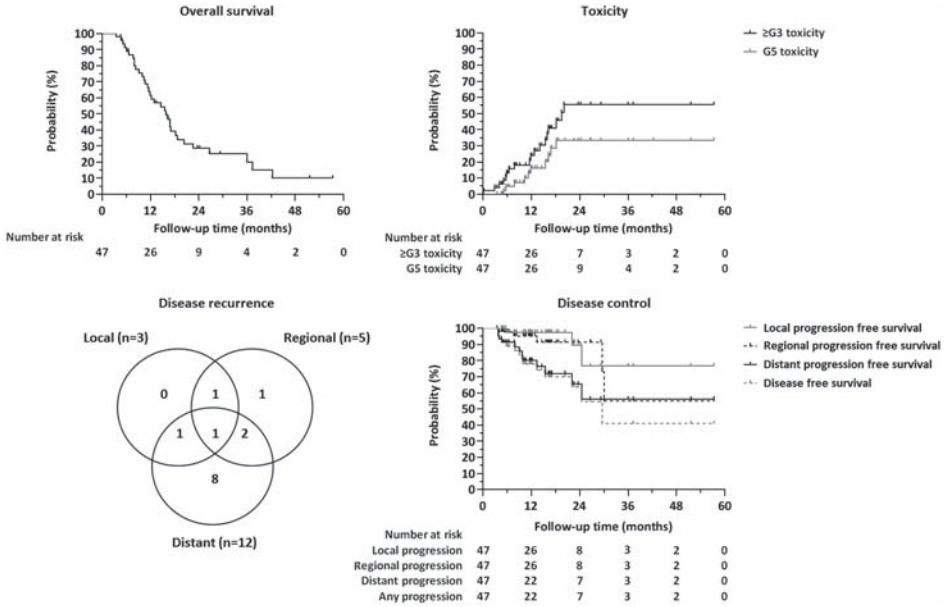


Figure 2 - Overall survival, toxicity, and disease control/recurrence of total cohort (n = 47)

Treatment toxicity

Long-term clinical information was available for 94% of patients, with detailed toxicity information lacking in three patients, who survived 3.5, 6.1 and 7.9 months, respectively. Causes of death in the latter three were metastatic NSCLC, "deterioration due to lung cancer", and lower gastrointestinal tract haemorrhage, with the latter occurring in a patient with a tumor in the left upper lobe. All three deaths were considered non-treatment related.

Development of possible acute or late grade 3 or higher toxicity was identified in a total of 38% of patients (n = 18) (Table 2). The actuarial incidence of the first event of G3 or higher toxicity was 23.9% at 12 months, and 55.5% at 24 months (Figure 2). Grade 4 toxicity was observed in one patient in whom severe hemoptysis developed in the absence of disease progression 4 months after an infectious pneumonia and endoscopic biopsy. This patient was admitted to the intensive care unit, intubated, and underwent succesful endoscopic intervention to control the haemorrhage. However, the patient elected to abstain from all further treatment, and died a few days later without evidence of tumor recurrence.

A total of 34 patients (72%) had died at the time of this analysis. No information on the cause of death was available for five patients who survived 15.9 to 42.3 months. Of the latter, two had manifested prior G3 toxicity and the remaining three had no G3 or higher toxicity. In total, seven deaths (15%) were scored by the clinician panel as being "possible" (n = 1) or "definitive" (n = 6) fatal lung haemorrhage, a further three deaths were attributed

to respiratory causes, and four other patients had a sudden death or a possible cardiac death (Supplemental Table 2). The remaining 15 patients died of lung cancer (n = 8) or as a result of causes unrelated to the treatment (n = 7). In total, 21% of all patients (n = 10) were considered by a clinician panel to have a possible (n = 2) or likely (n = 8) treatment-related death, with the actuarial incidence being 16.3% at 12 months (Figure 2, Supplemental Table 2, and Supplemental Figure 1). The mean age of these 10 patients scored as having a possible or likely treatment-related death was 75.8 years, and their mean age-adjusted CCI was 7.1. None had recorded locoregional relapse, but four patients had no follow-up scans performed within 6 months of death. The most frequent G5 toxicity was fatal lung haemorrhage (n = 7), which was observed within 6 months after the start of treatment in one patient, at 6 to 12 months in two patients, and after 12 months in four patients. One patient with sudden death may have had fatal lung haemorrhage that could not be verified, but the patient was nonetheless scored as having a possible G5 toxicity. Among the patients with a fatal lung haemorrhage, three (43%) had an endobronchial lesion identified before treatment, three (43%) had non-classifiable interstitial changes, and five (71%) used oral anticoagulant or antiplatelet drugs.

Table 2 - Details of severe (≥G3) toxicity

CTCAE v4.03	Adverse event	Number of patients (%)	First date after start radiotherapy
Grade ≥3	All	18 (38%)	0.2-41.3 mo
Grade 3		10 (21%)	0.2-41.3 mo
	Radiation pneumonitis	5 (11%)	4.1-14.1 mo
	Dyspnea or cough	3 (6%)	2.9-41.3 mo
	Chest wall pain	2 (4%)	4.1-16.0 mo
	Hemoptysis	2 (4%)	0.2-19.5 mo
Grade 4	Hemoptysis	1 (2%)	20.1 mo
Grade 5		10 (21%)	5.2-18.2 mo
Likely treatment-related	Fatal lung haemorrhage	6 (13%)	5.2-18.2 mo
	Euthanasia performed after severe dyspnea arising from bronchial obstruction and COPD	1 (2%)	11.3 mo
	Respiratory failure due to RP/pneumonia with septicaemia	1 (2%)	7.7 mo
Possible treatment-related	Multifactorial respiratory failure	1 (2%)	5.6 mo
	Sudden death, possibly associated with lung haemorrhage	1 (2%)	16.2 mo

Abbreviations: COPD = chronic obstructive pulmonary disease; CTCAE = Common Terminology Criteria for Adverse Events; mo = months; RP = radiation pneumonitis.

Dosimetric analysis

The initial treatment plan had been modified during treatment in four patients for reasons including tumor progression, PTV displacement due to pleural effusion, coughing episodes, and attempted improvement of esophageal sparing. In all four patients, the plan with the highest number of fractions was used to recalculate a new 12-fraction plan for dosimetric analysis. Dosimetric details are summarized and related to toxicity in Table 3, Figure 3, and Supplemental Figure 2. PTV point D_{max} was at least 123% of prescription dose in all patients, and no more than 140% in 64% of patients (median 138%, range 123%-154%). The D_{max} was 60 Gy or higher in 89% of patients for the main bronchi, in 43% for the trachea, and in 4% for the esophagus. The institutional esophageal D_{max} was exceeded in 13 patients, but the maximum $D_{0.5cc}$ was 47 Gy. There were no significant differences between patients with or without G3 or higher toxicity in the PTV D_{max}, and D_{max}, $D_{0.1cc}$, $D_{0.5cc}$, $D_{1.0cc}$, $D_{4.0cc}$, and $D_{5.0cc}$ for the trachea, main bronchi, esophagus, and the lung parameters reported in Table 3.

Table 3 - Dosimetric details

Dosimetric parameter	Median value (range) or number (%)	
	No ≥G3 toxicity seen (n = 29)	≥G3 toxicity seen (n = 18)
PTV D_{max} (Gy)	83.8 (73.6-92.1)	81.9 (77.9-86.0)
PTV $V_{95\%}$ ≥60 Gy	22 (75.9%)	15 (83.3%)
PTV $V_{99\%}$ ≥54 Gy	23 (79.3%)	15 (83.3%)
Main Bronchus D_{max} (Gy)	69.4 (1.2-82.4)	70.7 (55.3-84.0)
Main Bronchus D_{4cc} (Gy)	36.5 (0.8-63.3)	32.9 (8.3-73.6)
Trachea D_{max} (Gy)	59.0 (2.7-76.2)	33.2 (6.6-77.4)
Trachea D_{4cc} (Gy)	16.7 (2.1-65.1)	12.2 (2.22-61.9)
Esophagus D_{max} (Gy)	43.6 (19.7-62.4)	31.1 (18.3-64.3)
Esophagus D_{4cc} (Gy)	18.5 (12.8-33.6)	15.5 (10.8-41.2)
Total lung MLD (Gy)	6.0 (1.6-10.3)	6.3 (2.8-15.2)
Total lung V_{5Gy} (%)	26.0 (6.6-40.4)	24.8 (12.9-54.0)
Total lung V_{20Gy} (%)	8.8 (0-23.8)	11.4 (2.9-31.3)
Contralateral lung MLD (Gy)	2.1 (0.6-4.0)	2.0 (1.0-4.2)
Contralateral lung V_{5Gy} (%)	9.2 (1.4-32.1)	8.6 (0.4-29.5)

Physical doses were reported. Total lung was defined as total lung minus PTV. There were no significant differences between both groups. Abbreviations: D_{max} = maximum point dose; D_{4cc} = minimum dose received by 4 cc of organ at risk; MLD = mean lung dose; PTV = planning target volume; V_{5Gy} = volume of lung minus PTV receiving 5 Gy or more; V_{20Gy} = volume of lung minus PTV receiving 20 Gy or more.

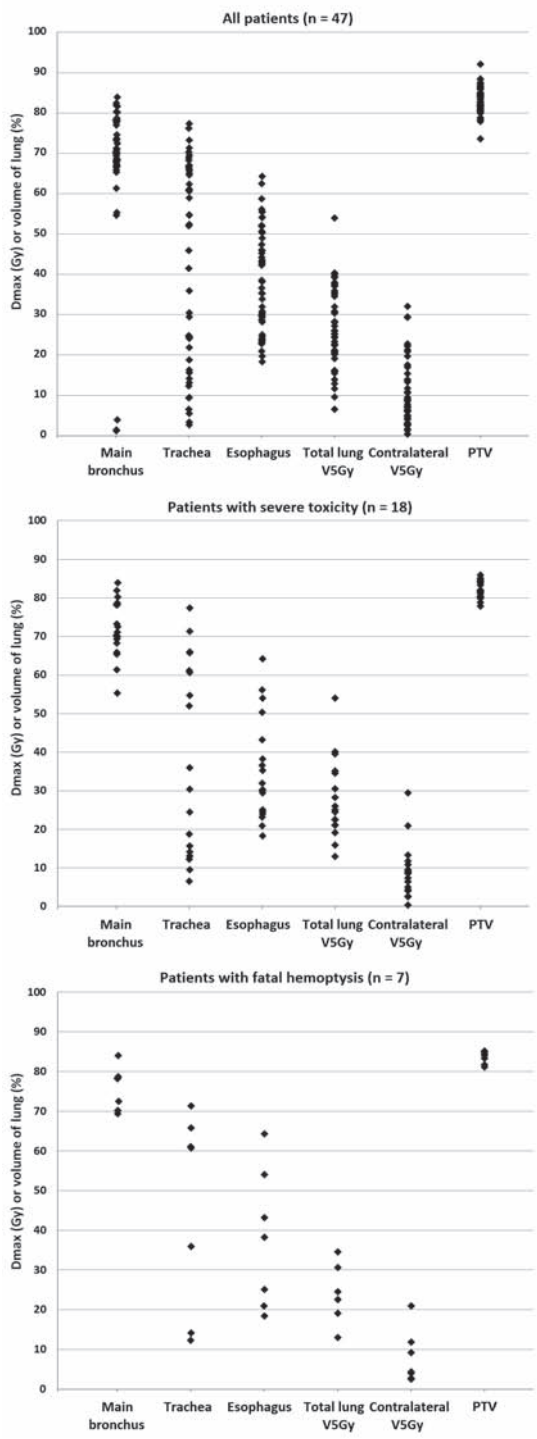


Figure 3 - Analysis of physical doses in all patients (n = 47), in patients with severe (≥G3) toxicity (n = 18), and in patients with fatal hemoptysis (n = 7).

DISCUSSION

We analyzed the results of 47 consecutive patients treated for ultracentral tumors, who were considered by our MDT board to be unsuitable for chemoradiotherapy, SABR or surgery. All received a 12-fraction scheme delivering heterogeneous doses of 5 Gy per fraction. Despite a median age-adjusted CCI of 7, all patients completed the planned treatment, and no 90-day post-treatment deaths were observed. The median OS was 15.9 months, and locoregional recurrences were infrequent; however, the observed high-grade toxicity on long-term follow-up merits further study.

In our initial analysis of the first 49 patients treated with this scheme, only 57% had an ultracentral tumor, and median follow-up was 6.8 months.[18] At the time of the initial report, the observed rate of G3 or higher toxicity was 20%. In the current analysis, which was limited exclusively to ultracentral tumors, and with longer follow-up, G3 or higher toxicity developed in 38% of patients, with 44% having their first G3 or higher toxicity event 12 or more months after commencing treatment. This highlights the importance of long-term follow-up after hypofractionated radiotherapy schedules.

Comparison of our results with other studies is difficult because of differences in patient selection and treatment schemes. The 46% of our cohort with a stage IIIA NSCLC had a median OS of 10.4 months, which is comparable to that of our patients with stage III NSCLC who were undergoing conventional radiotherapy (median OS 11.0 months).[19] Experience with SABR for ultracentral tumors is limited. One study reported significantly higher treatment-related mortality for tumors abutting the trachea, main bronchi, or lobar bronchi (22%) versus moderately central lesions (0%) after treatment with five fractions of 9 or 10 Gy.[20] The use of anti-vascular endothelial growth factor therapy in patients with an abutting tumor appeared as a possible risk factor for fatal haemorrhage.[20] However, a different definition for ultracentral tumors that also included tumors abutting lobar bronchi was used, and only T1/T2 tumors were studied. A second report on SABR (50 Gy in four or five fractions) did not observe significant differences in toxicity, local control, or overall survival between seven patients with ultracentral lesions and 27 with moderately central or 34 with peripheral tumors.[13]

The available literature suggests that tumor-related factors significantly influence the risk for the development of hemoptysis. In a prospective clinical trial, fatal hemoptysis was reported in 14% of patients with endobronchial tumors after conventional radiotherapy, and a similar incidence of 13% was seen after conventional radiotherapy in a large retrospective analysis.[11,12] A phase I trial in 79 patients with locally advanced NSCLC treated in 25 fractions observed that grade 4 (n = 1) or grade 5 (n = 5) toxicity was limited to patients whose tumors encased or abutted the main or proximal lobar bronchi, including three cases of fatal

hemoptysis.[9] Fatal hemoptysis has been associated with central tumor location, histologic diagnosis of squamous cell carcinoma, baseline tumor cavitation, and endobronchial tumor involvement, and an autopsy study reported fatal hemoptysis in 12% of patients with lung cancer.[21–24] In cases of NSCLC-related hemoptysis requiring intensive care admission, a majority (58%) had not received prior anticancer treatment, and 38% had only prior chemotherapy.[10] Again, a central tumor location (73%) and squamous cell carcinoma (52%) were more often present in patients in whom fatal hemoptysis developed.[10] Most of our patients had a histologic diagnosis of squamous cell carcinoma and endobronchial involvement, suggesting a predisposition to fatal hemoptysis. Furthermore, 71% of our patients in whom fatal hemoptysis developed had used oral anticoagulants or antiplatelet drugs during radiotherapy. However, as PTV D_{max} was 123% or more of prescription dose in all treatment plans, we cannot exclude that this contributed to the observed toxicity. We have since modified our protocol to specify the use of a homogeneous dose in the PTV, with a permitted D_{max} of 110% of the prescription dose instead of the 140% permitted in the patients treated in our report. Of note, there were no patients in our cohort with G3 or higher esophagitis and only one patient had clinically relevant bronchial obstruction. In retrospect, four of our patients were identified as having some degree of interstitial lung disease, with fatal lung haemorrhage developing in three of them. This highlights the need for further research in this group of patients.[14]

Some limitations of our study deserve mention. Many patients were unfit, and follow-up varied, limiting our ability to exclude recurrence as a source of hemoptysis. Similarly, retrospective scoring of toxicity and treatment-related death may be inaccurate, as the incidence of both sudden (cardiac) death is increased in patients with COPD alone.[25] In addition, absence of real-time verification of position of the tumor or OAR during treatment delivery could have led to either overestimation or underestimation of doses to OAR.

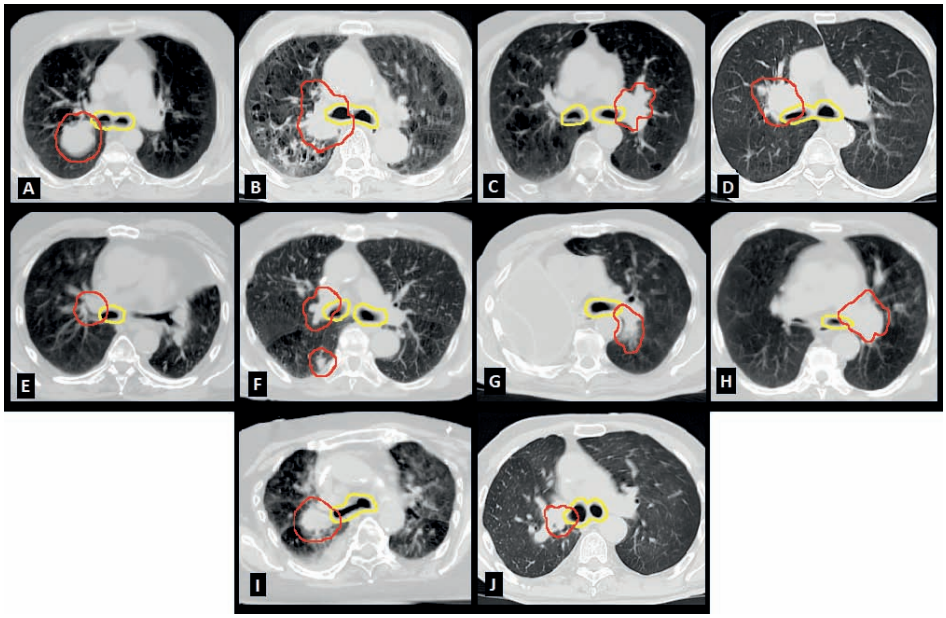
In conclusion, the 12-fraction hypofractionated schedule is a short, patient-friendly regimen with high compliance rates for patients who have limited treatment options. Long-term overall survival was good for this patient population. The incidence of fatal lung bleeding was comparable with that seen after conventional radiotherapy for endobronchial tumors, but the overall rate of fatal toxicity is nevertheless of potential concern. Until local control rates are better defined and the true risks of toxicity characterized in prospective studies, we will use this 12-fraction ultracentral schedule only in poor-risk patients in whom longer schedules are considered less feasible or declined by the patient. In addition, we have revised our protocol to ensure that a more homogeneous dose distribution is achieved within the PTV (D_{max} of 110%). All patients with such tumors will also be advised that our hypofractionated curative radiotherapy schedule delivering 2.5 to 3 Gy per fraction, represents the standard choice.

REFERENCES

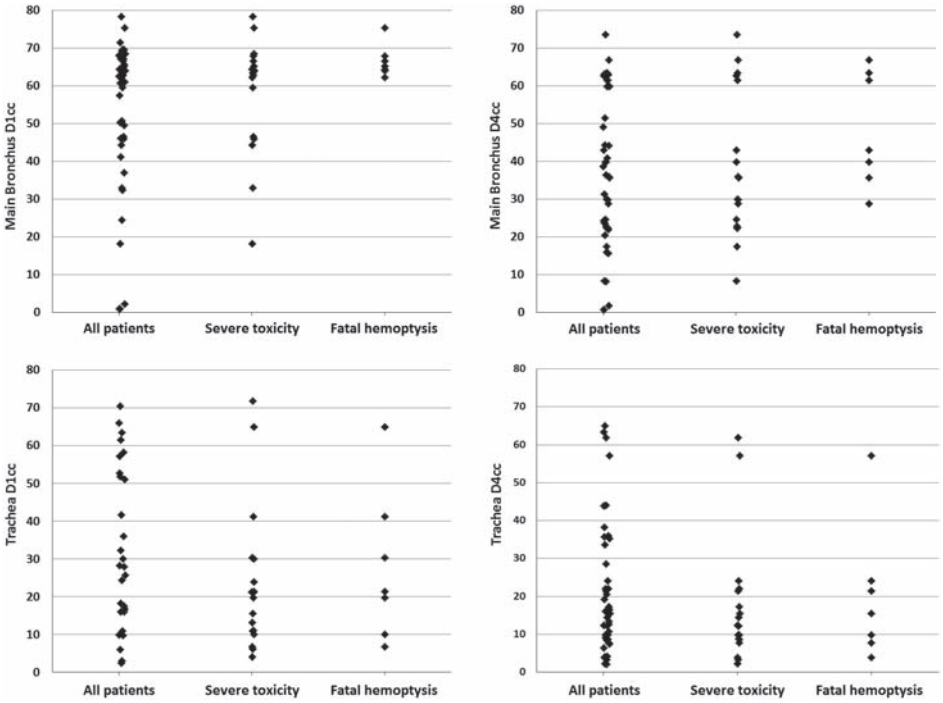
1. Rodrigues G, Choy H, Bradley J, et al. Definitive radiation therapy in locally advanced non-small cell lung cancer: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline. Pract Radiat Oncol. 2015;5(3):141-148.
2. Eberhardt WEE, De Ruysscher D, Weder W, et al. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Ann Oncol. 2015;26(8):1573-1588.
3. Kankerzorg in beeld 2014. Integraal Kankercentrum Nederland. Available at: www.iknl.nl. Accessed August 8, 2017.
4. Davidoff AJ, Gardner JF, Seal B, Edelman MJ. Population-based estimates of survival benefit associated with combined modality therapy in elderly patients with locally advanced non-small cell lung cancer. J Thorac Oncol. 2011;6(5):934-941.
5. Sigel K, Lurslurchachai L, Bonomi M, et al. Effectiveness of radiation therapy alone for elderly patients with unresected stage III non-small cell lung cancer. Lung Cancer. 2013;82(2):266-270.
6. Gabriel G, Barton M, Delaney GP. The effect of travel distance on radiotherapy utilization in NSW and ACT. Radiother Oncol. 2015;117:386–389.
7. Chang JY, Bezjak A, Mornex F. Stereotactic ablative radiotherapy for centrally located early stage non-small-cell lung cancer: what we have learned. J Thorac Oncol. 2015;10(4):577-585.
8. Vansteenkiste J, De Ruysscher D, Eberhardt WEE, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol.2013 Oct;24 Suppl 6:vi89-98.
9. Cannon DM, Mehta MP, Adkison JB, et al. Dose-limiting toxicity after hypofractionated dose-escalated radiotherapy in non-small-cell lung cancer. J Clin Oncol. 2013;31(34):4343-4348.
10. Razazi K, Parrot A, Khalil A, et al. Severe haemoptysis in patients with nonsmall cell lung carcinoma. Eur Respir J. 2015;45(3):756-764.
11. Huber RM, Fischer R, Hautmann H, Pöllinger B, Häussinger K, Wendt T. Does additional brachytherapy improve the effect of external irradiation? A prospective, randomized study in central lung tumors. Int J Radiat Oncol Biol Phys. 1997;38(3):533-540.
12. Langendijk JA, Tjwa MKT, de Jong JMA, ten Velde GPM, Wouters EFM. Massive haemoptysis after radiotherapy in inoperable non-small cell lung carcinoma: is endobronchial brachytherapy really a risk factor? Radiother Oncol J Eur Soc Ther Radiol Oncol. 1998;49(2):175-183.
13. Chaudhuri AA, Tang C, Binkley MS, et al. Stereotactic ablative radiotherapy (SABR) for treatment of central and ultra-central lung tumors. Lung Cancer. 2015;89(1):50-56.
14. Tekatli H, Senan S, Dahele M, Slotman BJ, Verbakel WFAR. Stereotactic ablative radiotherapy (SABR) for central lung tumors: Plan quality and long-term clinical outcomes. Radiother Oncol. 2015;117(1):64-70.
15. Underberg RWM, Lagerwaard FJ, Slotman BJ, Cuijpers JP, Senan S. Use of maximum intensity projections (MIP) for target volume generation in 4DCT scans for lung cancer. Int J Radiat Oncol Biol Phys. 2005;63(1):253-260.
16. Verbakel W, Senan S, Cuijpers JP, Slotman BJ, Lagerwaard FJ. Rapid delivery of stereotactic radiotherapy for peripheral lung tumors using volumetric intensity-modulated arcs. Radiother Oncol. 2009;93(1):122-124.

17. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996;17:343-346.
18. Bongers E, Dahele MR, Haasbeek CJ, et al. Hypofractionated Stereotactic Radiation Therapy for Large and Central Lung Tumors. Int J Radiat Oncol. 2012;84(3):S549-S550.
19. Van Reij EJF, Dahele M, van de Ven PM, et al. Changes in non-surgical management of stage III non-small cell lung cancer at a single institution between 2003 and 2010. Acta Oncol. 2014;53(3):316-323.
20. Haseltine JM, Rimner A, Gelblum DY, et al. Fatal complications after stereotactic body radiation therapy for central lung tumors abutting the proximal bronchial tree. Pract Radiat Oncol. 6(2):e27-33.
21. Ito M, Niho S, Nihei K, Yoh K, Ohmatsu H, Ohe Y. Risk factors associated with fatal pulmonary hemorrhage in locally advanced non-small cell lung cancer treated with chemoradiotherapy. BMC Cancer. 2012;12(1):27.
22. Kim Y-H, Kim E-Y, Ban H-J, et al. Risk Factors for Fatal Hemoptysis after Concurrent Chemoradiation Therapy in Patients with Non-Small Cell Lung Carcinoma. Chonnam Med J. 2010;46(1):19.
23. Reck M, Barlesi F, Crinò L, et al. Predicting and managing the risk of pulmonary haemorrhage in patients with NSCLC treated with bevacizumab: a consensus report from a panel of experts. Ann Oncol. 2012;23(5):1111-1120.
24. Nichols L, Saunders R, Knollmann FD. Causes of death of patients with lung cancer. Arch Pathol Lab Med. 2012;136(12):1552-1557.
25. McGarvey LP, Magder S, Burkhart D, et al. Cause-specific mortality adjudication in the UPLIFT® COPD trial: findings and recommendations. Respir Med. 2012;106(4):515-521.

SUPPLEMENTAL MATERIALS



Supplemental Figure 1 - CT scans of patients (PTV in red and main bronchus in yellow) with a possible or likely treatment-related death (n = 10). Patient details are presented in Supplemental Table 1 with corresponding letters.



Supplemental Figure 2 - Doses delivered to specific volumes of the main bronchus and trachea for the total cohort (n = 47), patients with severe (≥G3) toxicity (n = 18), and patients with a possible or likely fatal hemoptysis (n = 7).

Supplemental Table 1 - Radiotherapy fractionation schemes used at the VU University Medical Center

	Regimen	BED_{10}	Treatment time
Tumor <3 cm	3 fractions of 18 Gy	BED_{10} = 151.2 Gy	1.5 weeks
Tumor <3 cm and broad contact with chest wall and/or Tumor >3 cm, but <7 cm	5 fractions of 11 Gy	BED_{10} = 115.5 Gy	1.5-2 weeks
Central tumor adjacent to and/or with minimal overlap with plexus, hilus, stomach, pericardium, or mediastinum	8 fractions of 7.5 Gy	BED_{10} = 105 Gy	2.5 weeks
Tumor >7 cm and/or Central tumor with a substantial overlap with mediastinal structures and/or Presence of pathological ipsilateral mediastinal nodes	12 fractions of 5 Gy	BED_{10} = 90 Gy	3 weeks

Abbreviations: BED_{10} = biological effective dose with an α/β ratio of 10.

Supplemental Table 2 - Details of all patients with a respiratory, cardiac or sudden death, whose relationship with treatment was evaluated by a clinician panel.

Cause of death	Age (yrs)	Pre-treatment clinical details	Details of index lesion	Clinical outcomes	Remarks
Likely treatment-related death					
A. Fatal lung haemorrhage	60.6	WHO 1 CCI 7 COPD GOLD III AP use	T2bN0M0 RUL Path: unavailable PTV overlap: Main bronchus ITV/PTV: 66.8/127.1 cm^3	CT FU: 6.9 OS: 11.9 Relapse: - Other ≥G3 toxicities: -	
B. Fatal lung haemorrhage	79.1	WHO 1 CCI 6 COPD GOLD I ILD AP use	T4N0M0 RUL Endobronchial Path: SCC PTV overlap: Main bronchus and trachea ITV/PTV: 87.2/176.6 cm^3	CT FU: 9.3 OS: 10.4 Relapse: - Other ≥G3 toxicities: G3 RP	- Two possible primary lung tumors diagnosed in the contralateral lung during follow-up, and were untreated.
C. Fatal lung haemorrhage	84.4	WHO 1 CCI 7 COPD GOLD IV ILD	T3N0M0 LUL Endobronchial Path: unavailable PTV overlap: Main bronchus ITV/PTV: 40.8/95.7 cm^3	CT FU: 3.7 OS: 5.2 Relapse: - Other ≥G3 toxicities: -	
D. Fatal lung haemorrhage	70.2	WHO 1 CCI 7 COPD GOLD IV AP use	T3N0M0 RML Path: NSCLC NOS PTV overlap: Main bronchus and trachea ITV/PTV: 55.1/111.5 cm^3	CT FU: 9.2 OS: 18.2 Relapse: 9.0 (bone) Other ≥G3 toxicities: -	- Hospitalized 1 day before death with acute hemoptysis, and underwent bronchial artery embolization
E. Fatal lung haemorrhage	78.8	WHO 2 CCI 8 COPD GOLD III AP use	Recurrence RUL and hilar node Path: SCC PTV overlap: Main bronchus ITV/PTV: 19.5/56.8 cm^3	CT FU: 6.7 OS: 15.5 Relapse: - Other ≥G3 toxicities: -	- Prior lobectomy and multiple endobronchial treatments for tumor - Bronchoscopy with brush 3 weeks before death revealed only fungal infection on biopsy
F. Fatal lung haemorrhage	76.3	WHO 2 CCI 6 COPD GOLD II ILD OAC use	T1aN1M0 RLL Paravertebral lesion and hilar node Path: unavailable PTV overlap: Main bronchus ITV/PTV: 15.5/50.1 cm^3	CT FU: 6.8 OS: 16.8 Relapse: - Other ≥G3 toxicities: G3 RP	- Intra-ocular bevacuzimab administered during follow-up
G. Respiratory failure due to RP / pneumonia with septicaemia	73.9	WHO 1 CCI 9 COPD GOLD III	T4N0M0 LLL Endobronchial Path: SCC PTV overlap: main bronchus ITV/PTV: 19.4/52.5 cm^3	CT FU: 7.7 OS: 7.7 Relapse: - Other ≥G3 toxicities: -	- Prior pneumectomy and re-thoracotomy due to complications Bronchoscopic sputum evacuation 1 month before death

Supplemental Table 2 - Details of all patients with a respiratory, cardiac or sudden death, whose relationship with treatment was evaluated by a clinician panel. (*continued*)

Cause of death	Age (yrs)	Pre-treatment clinical details	Details of index lesion	Clinical outcomes	Remarks
H. Euthanasia performed after severe dyspnea, arising from bronchial obstruction and COPD	79.4	WHO 2 CCI 7 COPD GOLD IV Oxygen use	T4N0M0 LUL Endobronchial Path: SCC PTV overlap: main bronchus ITV/PTV: 61.5/136.1 cm^3	CT FU: 4.7 OS: 11.3 Relapse: 4.7 (liver) Other ≥G3 toxicities: G3 hemoptysis	
Possible treatment-related death					
I. Multi-factorial respiratory failure due to COPD, pneumonia, heart failure, pulmonary hypertension, and lung cancer	75.6	WHO 3 CCI 8 COPD GOLD II	T2bN1M0 RLL Peripheral lesion and hilar node Path: unavailable PTV overlap: main bronchus ITV/PTV: 116.7/227.7 cm^3	CT FU: 4.1 OS: 5.6 Relapse: - Other ≥G3 toxicities: -	
J. Sudden death, possibly associated with lung haemorrhage	79.8	WHO 0 CCI 6 COPD GOLD II	Recurrence RML Endobronchial Path: SCC PTV overlap: main bronchus ITV/PTV: 7.2/23.9 cm^3	CT FU: 13.3 OS: 16.2 Relapse: - Other ≥G3 toxicities: -	- Prior sleeve lobectomy
Unlikely treatment-related death					
K. Acute myocardial infarction	62.9	WHO 1 CCI 7 COPD GOLD III ILD OAC use	T4N0M0 LUL Path: SCC PTV overlap: main bronchus and trachea ITV/PTV: 84.2/166.6 cm^3	CT FU: 4.4 OS: 4.7 Relapse: - ≥G3 toxicities: -	- Chemotherapy up to 1 month of start RT - Prednisone and antibiotics up to RT due to subtotal atelectasis - Emergency endobronchial debulking during RT due to total atelectasis - No pulmonary complaints during a period of a few months before death
L. Sudden death	83.8	WHO 2 CCI 7 COPD GOLD II OAC use	T2aN2M0 LUL Endobronchial Path: unavailable PTV overlap: main bronchus and trachea ITV/PTV: 35.9/104.5 cm^3	CT FU: 12.9 OS: 14.6 Relapse: - ≥G3 toxicities: -	

Supplemental Table 2 - Details of all patients with a respiratory, cardiac or sudden death, whose relationship with treatment was evaluated by a clinician panel. (*continued*)

Cause of death	Age (yrs)	Pre-treatment clinical details	Details of index lesion	Clinical outcomes	Remarks
M. Sudden death	77.5	WHO 1 CCI 6 COPD GOLD II AP use	T3N0M0 RML Endobronchial Path: SCC PTV overlap: main bronchus and trachea ITV/PTV: 80.9/155.5 cm^3	CT FU: 9.7 OS: 10.6 Relapse: - ≥G3 toxicities: -	- Prior lobectomy due to primary NSCLC RUL
N. Sudden death	71.6	WHO 1 CCI 9 COPD GOLD II AP use	Recurrence LUL Endobronchial Path: unavailable PTV overlap: main bronchus ITV/PTV: 8.1/27.8 cm^3	CT FU: 22.2 OS: 26.7 Relapse: ≥G3 toxicities: G3 RP	- Prior endobronchial treatment for same lesion

Staging was based on the 7th edition of the TNM. Abbreviations: AP = antiplatelet drug; CCI = Age-adjusted Charlson Comorbidity Index; CT FU = follow-up with a CT in months; ILD = interstitial lung disease; ITV = internal target volume; LLL = left lower lobe; LUL = left upper lobe; Path = pathological diagnosis; PTV = planning target volume; Relapse = any disease recurrence, in months after start of index treatment; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; RP = radiation pneumonitis; RT = radiotherapy; RUL = right upper lobe; OAC = oral anticoagulant drug; OS = overall survival in months; SCC = squamous cell carcinoma; yrs = years.